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The Surgical Treatment of Wilms' Tumor:

Results of the National Wilms' Tumor Study

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Surgical data derived from the 606 patients in the National Wilms' Tumor Study have been analyzed to determine the effect of surgical technique on results of treatment. In addition to surgical excision of the tumor, patients were treated with chemotherapy and radiation therapy according to the study protocol. Under these controlled conditions, certain aspects of surgical technique which have traditionally been thought to be important for success appear to be irrelevant. Physical characteristics of the tumor, preoperative rupture and vascular invasion by tumor were not associated with higher relapse rates. Large tumors, those with capsular infiltration, and tumors with spread to lymph nodes had a higher recurrence rate. Operative spill increased the chance of abdominal recurrence. There was no evidence that early ligation of the renal vein was of value in prevention of recurrence, nor was incomplete removal of tumor associated with an increase in relapse rate. Although several critical factors of surgical technique were not studied, it is clear that others are not significant and need not be continued.

THE NATIONAL WILMS' TUMOR STUDY (NWTS) was initiated in 1969 by three large cancer study groups as a prospective study to compare treatment programs for safety and effectiveness. Sixty-five institutions participated in the study. For patients under two years of age with tumor confined to the kidney and completely resected (Group I) it was determined that radiation therapy did not improve the excellent cure rate achieved by chemotherapy. For children with non-metastatic disease that had already spread within the abdomen (Groups II and III) the combination of actinomycin-D and vincristine was more effective than either alone.[2]

Details of surgical technique are also thought to be of importance in the ultimate outcome in patients with Wilms' Tumor, and the clinical–pathologic Grouping (Table 1), which determines the drug and radiation therapy to be given, depends in large part on the surgeon's findings. Surgical data derived from the NWTS have been examined to determine the impact on relapse and survival of several aspects of surgical technique which have traditionally been thought to be important for success. This analysis considers the surgical variables from two points of view: What the surgeon *finds* (gross tumor characteristics) and what the surgeon *does* (operative procedure and technique).

Methods

From October 1, 1969 to December 31, 1973, 606 patients were registered in the National Wilms' Tumor Study. 359 patients who were randomized and treated according to the NWTS protocol for each Group, and

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TABLE 1. *National Wilms' Tumor Study Clinical Groupings*

GROUP I—Tumor Limited to Kidney and Completely Resected
The surface of the renal capsule is intact. The tumor was not ruptured before or during removal. There is no residual tumor apparent beyond the margins of resection.

GROUP II—Tumor Extends Beyond the Kidney but is Completely Resected
There is local extension of the tumor; *i.e.*, penetration beyond the pseudocapsule into the perirenal soft tissues, or periaortic lymph node involvement. The renal vessels outside the kidney substance are infiltrated or contain tumor thrombus. There is no residual tumor apparent beyond the margins of resection.

GROUP III—Residual Nonhematogenous Tumor Confined to Abdomen
Any one or more of the following occur:
1) The tumor has been biopsied or ruptured before or during surgery;
2) there are implants on peritoneal surfaces;
3) there are involved lymph nodes beyond the abdominal periaortic chains;
4) the tumor is not completely resectable because of local infiltration into vital structures.

GROUP IV—Hematogenous Metastases
Deposits beyond Group III; *e.g.*, lung, liver, bone and brain.

GROUP V—Bilateral Renal Involvement Either Initially or subsequently.

The patient's group is decided by the surgeon in the operating room, and is confirmed by the pathologist. If the histological diagnosis and grouping will take more than 48 hours, the surgical grouping stands, the patient is registered and started on treatment.

an additional 94 patients who were followed on the study protocol without randomization were analyzed. The details of this study and the results have been previously published.[2] Surgical check sheets were completed on all patients on study, giving information as to the type of incision, physical characteristics and location of the tumor, whether it invaded other organs, the degree of vascular invasion, apparent lymph node involvement, whether nodes were removed, completeness of tumor removal, and whether the renal vein was ligated before tumor mobilization. These check sheets as well as copies of the operative notes have been reviewed by the surgical members of the NWTS Committee, and representative microscopic slides from each tumor have been reviewed by the NWTS pathologist (Dr. J. B. Beckwith).

Because operations were performed by surgeons with widely varying backgrounds, there were many differences in surgical technique. Furthermore, certain observations depend upon the accuracy and thoroughness of the operative notes; some were incomplete. It should be emphasized that during the study there was no control over some aspects of operative treatment which may be crucially important: gentle technique, adequate exposure, thorough exploration, and complete excision. It is probable, but not established, that these variations in technique were randomly distributed among all patients on study and thus do not have a direct effect on treatment comparisons.

Since complete data regarding all variables was not available for every patient on study, the "denominator" (number of patients for whom the characteristic is known) varies among the categories studied. For example, although data on tumor weight is available for 409 patients, lymph nodes were removed and available for examination in only 245 patients. However, relapse-free survival (RFS) data is only compared in Groups I–III patients who were followed for at least two years operation, a total of 361 patients. Some survival results for 65 Group IV patients followed at least two years are also presented.

Results

What the Surgeon Finds

Gross morphologic characteristics. Except for size, the physical characteristics of the tumor appear to have little effect on later outcome. There is no statistically significant difference in relapse-free survival (RFS) in comparable treatments groups whether the tumor was diffusely distributed throughout the kidney or well localized to one or the other pole. Similarly, there was no difference in outcome according to whether the tumor was unicentric or multicentric in origin, nodular or smooth, or hard or soft in consistency (Table 2). *Soft* tumors were associated with a higher incidence of pre-operative rupture (6.9%) than hard tumors (0.5%), as well as increased frequency of spillage of tumor at the time of operation (21.8% vs. 11.7% for hard tumors). However, neither of these factors adversely affected the relapse-free survival. In general, the gross configuration and consistency of the tumor are poor guides to outcome.

TABLE 2. *Effect of Tumor Characteristics on Outcome*

Characteristics	Total	Relapse Free	%	Alive	%
Diffuse*	137	100	73.0	115	83.9
Localized	182	134	73.6	157	86.3
Unicentric	179	134	74.9	157	87.7
Multicentric	40	28	70.0	32	80.0
Nodular	109	76	69.6	90	82.6
Smooth	151	117	76.5	134	88.7
Hard	173	125	72.3	150	86.7
Soft†	150	106	70.7	124	82.7

* Cases termed diffuse and those with tumor in both poles.
† Includes cases with a tumor having both hard and soft tumor components.
None of these differences are significant.

TABLE 3. *Effect of Capsular Infiltration*

	Total	Relapse Free	%	Alive	%
Capsular Infiltration, Group II*	35	21	60.0	28	80.0
No capsular Infiltration, (Group I)	140	113	80.7	128	91.4

* Patients who are placed in Group II *solely* because of capsular infiltration.
$p = 0.02$ (relapse). $p = 0.10$ (survival).

Capsular infiltration. Evidence of infiltration of the capsule, however, is significant, and, as the *only* manifestation of tumor spread, carried a lowered relapse-free survival rate (60.0%) than that seen in patients with similar tumors that have not penetrated the capsule (80.7%) (Table 3). Unfortunately, the surgeon's accuracy in this assessment was limited. If the surgeon judged the capsule to be penetrated, he was right 70.9% of the time (39 of 55 specimens reported). On the other hand, 42 of 156 tumors (26.9%) which the surgeon thought had an intact capsule proved to have microscopic evidence of penetration when examined by the pathologist. Thus, although capsular invasion is of significance in prognosis, surgical assessment of this important variable is not very reliable.

Tumor size. Older patients had larger tumors and larger tumors tended to be in patients with more advanced disease (Fig. 1). The RFS was significantly higher in patients with tumors weighing less than 375 grams (83.5%) than in patients with larger tumors (66.8%) (p = .002). Most patients with smaller tumors were in the first year or two of life when the prognosis is better. However, even among patients under two, those with smaller tumors fared better (Table 4).

Preoperative rupture. A tumor was characterized as having ruptured preoperatively if the patient was found to have free blood or floating tumor in the peritoneal cavity, gross rupture through the capsule, or peritoneal implants of tumor. There were 19 of these patients. Although it has generally been assumed that preoperative rupture, with the obvious potential for spreading tumor cells widely, carries a poor prognosis, such was not the case. The one patient with peritoneal implants later succumbed. Of the remaining 18, however, only one has subsequently developed recurrence of tumor within the abdomen. The RFS in this group was 61.5%, which is not significantly different from those without preoperative rupture (74.8%). Thus, preoperative rupture does not necessarily carry a poor prognosis (unless there are peritoneal implants), nor is it associated with a particularly high risk of intra-abdominal recurrence. These results differ from initial results reported by Lemerle, et al. where tumor rupture decreased the RFS

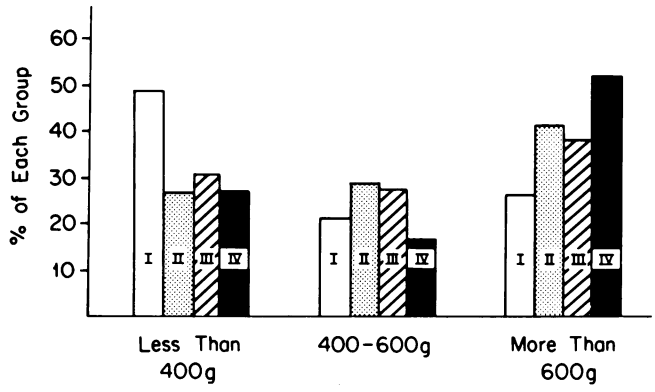

FIG. 1. Relationship of tumor weight to group. Disseminated tumors are more likely to be large.

by half.[3] Later reports from the same group also showed no effect on RFS at 18 months.[4]

Lymph node spread. When the surgeon is confident that the lymph nodes are negative, the pathologist almost always agrees (96.0%). However, when lymph nodes are assessed as containing tumor by the surgeon, the pathologist often (39.3%) fails to find involvement by microscopic examination. Spread to lymph nodes significantly alters the prognosis in patients with Wilms' tumor. Seventy-two per cent of patients who have no evidence of tumor in lymph nodes are free of disease at two years. If hilar lymph nodes alone are involved, the RFS drops to 56.7%. If both hilar and periaortic lymph nodes are found to harbor tumor deposits, only 33.3% of these patients remain free of tumor (Table 5). These results are similar to those reported by others.[3]

Vascular invasion. Tumor was present in the renal vein or inferior vena cava in 37 patients, but was not associated with a poorer outcome. In Groups II and III patients, RFS was identical whether or not there was tumor in the renal vein. It appears that chemotherapy effectively handled blood-borne tumor.

Invasion of the liver. Liver involvement, either by

TABLE 4. *Relationship of Tumor Weight to Outcome*

	Less Than 375 g			More Than 375 g		
Age	Total	Relapse Free	%	Total	Relapse Free	%
0–23 mo.	54	50	92.6	60	47	78.3
24–47 mo.	33	24	72.7	91	56	61.5
48 + mo.	16	12	75.0	75	48	64.0
Age	Total	Alive	%	Total	Alive	%
0–23 mo.	54	52	96.3	60	50	83.3
24–47 mo.	33	30	90.9	91	72	79.1
48 + mo.	16	15	93.8	75	59	78.7

Top half of table: p = .014 (adjusted for age).
Bottom of table: p = 0.003 (adjusted for age).

TABLE 5. *Effect of Lymph Node Involvement on Outcome*

Pathologic Examination	Total	Relapse Free	%	Alive	%
Not examined	105	84	80.0	95	90.5
Negative	206	149	72.3	177	85.9
Hilar nodes positive	30	17	56.7	22	73.3
Hilar & aortic positive	9	3	33.3	3	33.3

p = 0.02 all positive vs. negative (relapse).
p = 0.002 all positive vs. negative (survival).

direct extension or metastatic spread, lowers the prognosis significantly. Only three of seven patients with liver involvement in groups II and III were relapse-free survivors (42.9%) compared to 255/350 (72.9%) of patients without liver tumor. These differences held with group IV patients as well (4/14 = 28.6% survivors vs. 28/49 = 57.1%). Using a combined statistical analysis[5] it is clear that liver involvement significantly alters outcome (p = 0.05). Unfortunately, resection of the invading or metastatic tumor in the few cases in which it was tried, did not effect cure.

What the Surgeon Does

Incision. Whether the incision was vertical, transverse, or thoraco-abdominal made no difference. Surgeons who are experienced in the treatment of Wilms' tumor tend to use generous transverse incisions, with thoracic extensions if necessary. Operative spillage was no more frequent with one type of incision than another, nor was the incidence of incomplete removal of tumor. The RFS in comparable treatment groups did not vary according to incision.

Lymph node resection. Removal of hilar or periaortic nodes was not associated with any significant differences in the RFS in patients in comparable treatment groups (Table 6). More than two-thirds of patients had hilar or periaortic nodes removed, but the basis for the decision to perform lymphadenectomy is unknown in most cases. The NWTS surgical guidelines neither required nor prohibited lymph node dissection, leaving the decision to the judgement of the operating surgeon. In five of the six groups represented in Table 6, the relapse-free survival was actually higher in patients who did not have lymph node dissection carried out. This most probably reflects the fact that surgeons were more apt to carry out a node dissection when the nodes appeared positive grossly. Since these results do not reflect a controlled study of this question, all that can be concluded is that the data provide no evidence that lymph node resection does or does not alter the outcome in Wilms' Tumor.

Operative spillage. How important is it for the surgeon to take care not to spill tumor in the process of removing it? In 57 of 343 patients (16%) with complete follow-up, the operative note indicated that there was major or minor spillage of tumor, or that tumor was cut across during resection. The differences in overall RFS rate between patients with and without spill are only suggestive (36/57 = 63.2% vs. 214/286 = 74.8%, p = 0.10). However, abdominal recurrences were almost twice as frequent in patients with operative spill (p = 0.05), and this led to a higher mortality rate (22.8%) (p = 0.07) (Table 7).

Prior ligation of the renal vein. Seventy per cent of surgeons indicated that they ligated the renal vein before mobilizing the tumor. Many ligated the renal artery at the same time, others did not. The size of the tumor did not materially influence the surgeon's choice, nor was ligation more common in one Group than another. Early ligation of the renal vein had no discernible effect on ultimate outcome. Relapse rates were actually higher in patients with prior ligation, though not significantly. This lack of difference held regardless of the patient's age or Group.

Removal of tumor from the renal vein or inferior vena cava. It has already been noted that in the analysis of the entire group of patients, the presence of tumor in the renal vein or IVC did not affect outcome. Unfortunately, operative removal of tumor from the vein was not carried out in enough patients to permit evaluation of its effect on RFS.

Complete removal of tumor. Surgeons indicated on the report form whether or not all tumor seemed to be grossly removed. Surprisingly, leaving small amounts of tumor behind was not associated with a significant difference in RFS in comparable treatment groups. It should be noted that patients with tumor invasion of surrounding tissues were in Groups III or IV and thus received the full extent of chemotherapy and radiation treatment. As a sole variable, failure to remove all of the tumor was not associated with any difference in outcome (Table 8). Biopsy of the tumor in the course of the operation was reported too infrequently (three patients) to assess its effect on survival.

TABLE 6. *Effect of Lymph Node Resection on Outcome*

		Hilar			Aortic		
	Resected	Total	Relapse Free	%	Total	Relapse Free	%
Group I	Yes	108	87	73.8	83	64	77.1
	No	42	31	80.6	66	55	83.3
Group II–III A & B	Yes	89	47	52.8	72	35	48.6
	No	20	16	80.0*	40	29	72.5*
Group II–III C	Yes	60	47	78.3	51	41	80.4
	No	20	17	85.0	29	23	79.3

* p = .05.

It is evident from these data, as well as that pertaining to the effect of preoperative rupture, that although gross removal of the bulk of the tumor is probably important, adjuvant treatment is capable of destroying the remaining cells when they are relatively few in number. Similar findings were apparent in the NWTS analysis of bilateral tumors.[1]

Discussion

Collection of data from a large number of patients undergoing treatment for Wilms' Tumor in a controlled clinical study has made possible the analysis of the influence of a number of anatomic and technical variables on outcome. Although there were recommendations for the conduct of the operation, surgical technique was not controlled as closely as was the administration of chemotherapy and radiation therapy. Accordingly, variations in surgical technique are analysed retrospectively.

It has long been recognized that certain obvious factors such as the age of the patient and the extent of tumor spread profoundly affect the outcome, regardless of treatment. Conversely, progress in chemotherapy and radiation therapy have so improved the survival in Wilms' tumor for previously high-risk patients that their outlook is now approaching if not equal to that of the most favorable ones several decades ago. The three-year survival rate in the NWTS for children in groups II and III receiving radiation therapy and both actinomycin-D and vincristine is 84.3%.[2]

Certain factors emerge as clearly favorable, others unfavorable, and some are apparently irrelevant. Patients under the age of two with tumors that have no evidence of capsular invasion or local spread have an excellent prognosis.[2] A worse than average outcome is associated with large tumors, lymph node involvement, distant metastatic spread, capsular infiltration, and liver involvement, whether direct or metastatic.

TABLE 7. *Operative Spillage*

	Neither Oper. Spill or Pre-op Rupture		Operative Spill	
	No.	%	No.	%
No. of Patients	286	100.0	57	100.0
Relapsed	72	25.2	21	36.8*
Contralateral Kidney	10	3.5	1	1.8
Other Abdominal Site	38	13.3	14	24.6†
Lung	57	19.9	16	28.1
All Other (Brain, Bone, etc.)	19	6.6	5	8.8
Died	36	12.6	13	22.8‡

* $p = 0.10$ † $p = 0.05$ ‡ $p = 0.07$.

TABLE 8. *Effect of "Complete Removal" on Outcome*

	Complete Removal			Incomplete Removal		
	Total	Relapse Free	%	Total	Relapse Free	%
Operative spillage	36	23	63.9	13	10	76.9
IVC involved	7	6	85.7	3	3	100.0
Renal vein involved	13	10	76.9	3	2	66.7
Adrenal involved	12	8	66.7	3	1	33.3
Pre-op rupture	5	3	60.0	6	4	66.7
Any of the above*	59	38	64.4	23	15	65.2

* Some patients had spread to two or more locations.

Operative spill increases the chance of abdominal recurrence.

A number of factors seem to have no bearing whatever on outcome. These include whether the tumor is diffuse or localized within the kidney, uni- or multicentric, or soft or hard. Preoperative rupture and gross tumor involvement of the renal vein or inferior vena cava were not of significance in the outcome of these patients.

The surgeon must take care to remove the tumor so as not to rupture it and spill tumor. The other details of the surgical approach that were studied did not demonstrably alter the outcome of these patients. There is no evidence that early ligation of the renal vein prevents recurrence. Most surprising, small amounts of visible tumor left behind did not result in a lower relapse-free survival rate compared with patients whose disease extended beyond the kidney but was "completely removed." There is therefore, no evidence from this study that heroic or destructive efforts to remove the last vestige of tumor (such as resecting parts of normal organs) is desirable or beneficial.

None of these technical factors were studied in a controlled fashion, so subtle differences may well have been obscured. On the other hand, few striking correlations have emerged. It is probable that the extraordinary effectiveness of chemo- and radiotherapy compensates for some of the deleterious effects of breaches in surgical technique.

It should not be inferred from the results of these analyses that details of surgical technique are irrelevant, or that careless, poorly planned operations by the inexperienced are appropriate. The data reported here represent the results of a carefully controlled clinical trial. All patients benefited from systematic, up-to-date therapy, and from the combined attention of specialists, including surgeons, who are familiar with the problems of childhood cancer. Similar results will not be obtained if treatment is haphazardly given by inexperienced personnel.

If anything, the results of this study indicate that

in the future the surgeon's approach to the patient with Wilms' tumor must be *more* sophisticated, not less. Grouping depends largely upon the surgeon's findings. Errors will result in inadequate or excessive treatment. The abdomen must be carefully explored through an ample transperitoneal incision. There is no justification for an extraperitoneal flank incision. The surgeon must search for evidence of spread to other organs, particularly the liver and the opposite kidney and to lymph nodes. This cannot be accomplished through a flank "nephrectomy" incision.

It is not acceptable just to "get the tumor out." The tumor must be removed with great care to avoid spill or damage to other organs. Inadvertent cutting across tumor, or spillage of tumor because of rough handling, not only significantly increases the mortality risk for the patient, in some cases it will alter the grouping unfavorably. Thus the patient will be subjected to more extensive chemotherapy and radiation therapy with all of the associated side effects, complications, and increased mortality risk.

Careful assessment of lymph node involvement is essential, since the extent of spread to lymph nodes is clearly correlated with outcome. Although the desirability of performing a total periaortic lymphadenectomy has not been established, the importance of knowing the extent of lymph node involvement has been. The surgeon should carefully examine all the hilar and periaortic nodes and excise any that are suspicious, labeling each as to site of origin.

Since the overwhelming majority of relapses in these patients are caused by pulmonary metastases, the surgeon should direct his efforts to maneuvers which might minimize this possibility. Gentleness in manipulation of tumor and meticulous control of venous outflow may be critical factors.

It is clear that several traditional technical aspects of the resection of Wilms' tumor have little evidence in their support and are probably unnecessary. It is equally clear that other technical considerations are crucially important. Since the major thrust of advances in the administration of chemotherapy and radiation therapy has been to tailor the treatment to the extent of the patient's disease, careful grouping is essential to avoid giving the patient either too much or too little. The surgeon bears a heavy responsibility to assess the extent of tumor spread accurately and to extirpate the tumor without causing further spread or damage to normal organs.

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